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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/900,715	07/06/2001	Keith D. Allen	R-775	3970

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EXAMINER	
WOITACH, JOSEPH T	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 02/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/900,715	ALLEN, KEITH D.	
	Examiner	Art Unit	
	Joseph T. Woitach	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This application filed July 6, 2001, claims benefit to provisional applications 60/216,104, filed July 6, 2000, and 60/223,386, filed August 7, 2000.

Applicants' amendment filed October 24, 2003, has been received and entered. The specification has been amended. Claims 1-25 have been canceled. Claims 26-36 have been added. Claims 26-36 are pending.

Election/Restriction

Applicants have not set forth any further traversal of the restriction requirement. Applicant's election with traverse of Group I drawn to a targeting construct comprising a polynucleotide sequence homologous to the sequence encoding protein phosphatase 2C and a selectable marker and the transgenic animal generated with said construct, and method of producing said construct in Paper No. 9 was acknowledged.

It is noted that all newly added claims 26-36 are directed to the elected invention. Upon review of the subject matter set forth in the newly added claims and in light of the teaching of the instant specification and art of record, the prior rejection have been withdrawn and new rejections have been set forth below.

Claims 26-36 are pending and currently under examination.

Specification

It is noted that the amendment to the specification has put the application in sequence compliance with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 26-36 are rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility.

The specification asserts that the transgenic mouse and cell can be used as models for diseases, disorders or conditions associated with phenotypes relating to a disruption in a protein phosphatase 2C gene. The model can be used to identify potential therapeutic agents for treating such diseases. The specification does not identify a single disease, disorder or condition known to be associated with either aberrant expression of protein phosphatase 2C or expression of aberrant protein phosphatase 2C. Before using the claimed mouse and cells for such a purpose, one would first be required to identify a disease, disorder or condition associated with either aberrant expression of protein phosphatase 2C or expression of aberrant protein phosphatase 2C Such activity constitutes using the invention as an object of research in order to determine a use

for the invention, and does not meet the requirement for a specific and substantial utility. *Brenner v. Manson*, 148 USPQ 689 (US SupCt. 1966).

The specification asserts that a mouse with a protein phosphatase 2C disruption "exhibits sensitivity to pain opposite or consistent with one or more symptoms of a disease or condition associated with all types of pain." This appears to leave open whether the disruption has any effect whatsoever on pain sensitivity. The specification also asserts that the transgenic mouse can be used to screen potential therapeutic agents for their ability to modulate a pain response. The specification describes assays for determining sensitivity to pain, and prophetically carrying out such assays on transgenic mice and comparing the results to wild type mice. However, the specification provides no evidence that transgenic mice with a disruption in protein phosphatase 2C respond any differently to pain than do wild type control mice. Since any mouse can be used in the disclosed pain assays to screen potential therapeutic agents for their ability to modulate a pain response, and the specification fails to provide any evidence that the claimed transgenic mouse would respond differently than a wild type mouse in any useful way, this alleged use is non-specific to the claimed mouse and fails to meet the requirement for a specific and substantial utility.

The specification discloses that the specific transgenic mice made by disrupting the protein phosphatase 2C genes in an ES cell of a 129/OlaHsd mouse, and crossed into a C57BL/6 background displayed a pre-pulse inhibition to acoustic startle response (PPI), with a 100 dB pre-

pulse, that was statistically-significantly lower than the PPI of an unspecified wild-type control mouse. The specification states that the lower PPI "may reflect a loss of sensorimotor gating as seen in human schizophrenics, or a reduced ability to process external information." Based upon this experimental result, the specification asserts that the transgenic mutant mice may be used to screen potential anti-psychotic agents or other known compounds for their use in treating schizophrenia. Presumably, potentially useful compounds would be those which increase the PPI of the transgenic mouse. The specification does not identify any compound that would increase PPI in the transgenic mice, much less compounds that were known to be useful for treating schizophrenia.

This asserted utility is speculative at best, while it is known that human schizophrenics display a PPI deficit, several other distinctly different human disorders were also known to be characterized by a PPI deficit, including schizophrenic personality disorder, obsessive-compulsive disorder, Huntington's disease, nocturnal enuresis, attention deficit disorder, and Tourette's syndrome (Swerdlow et al., Schizophrenia Bulletin 24 (2): 285-301, 1998; Paylor et al. Psychopharmacology 132: 169-180, 1997; Geyer et al. Molecular Psychiatry 7 (10) : 1039-1053, 2002). The specification lists a variety of symptoms of schizophrenia, including motor disturbances, stupor, negativism, rigidity, excitement, inability to care for personal needs, decreased sensitivity to painful stimulus, delusion, anxiety, anger, violence, aggression, argumentative behavior, incoherence, etc. However, the specification does not report any other

phenotypes of the claimed transgenic mouse that would be consistent with human schizophrenia. Example 3 describes the mice being observed for general behavioral characteristics, including grooming, behavior toward siblings, activity level, movement, and general physical condition; the working example describes the mice being tested for pain sensitivity using the hot plate test; describes the mice being subjected to an open field test, which measures anxiety and locomotion; and describes the mice being subjected to a tail suspension test, which measures depression. No deviation from wild type was reported for any of these assays. In summary, there is no supporting evidence in the specification that the claimed mouse suffers from a condition similar to schizophrenia in humans. Furthermore, as acknowledged in the specification, a PPI deficit may reflect an reduced ability to process external information. As disclosed by Geyer (page 1040), it was known in the art that differences in hearing influences PPI. Thus, it is unclear whether the PPI reduction reflects a difference in sensorimotor gating or with hearing ability, which would have nothing to do with schizophrenia.

Geyer discloses that after the instant application was filed, no genes had been identified whose function was associated with schizophrenia, and that "it has been impossible to evaluate PPI is a mutant mouse created with a mutation in a gene known to cause schizophrenia" (para. bridging pages 1043-1044). There is no evidence of record that aberrant expression of protein phosphatase 2C or expression of aberrant protein phosphatase 2C is associated in any way in schizophrenic humans. While mutant mice, including knock-out mice, have been useful in

identifying genes involved in regulating sensorimotor gating, there is no evidence of record that mutants showing an altered PPI have been useful for identifying medications for treating schizophrenia, or any other psychotic disorder (see Swerdlow and Geyer). While the reduced PPI of the claimed mouse may be of scientific interest in studying the relationship, if any, between protein phosphatase 2C function sensorimotor gating, using the mouse in such research activity constitutes using the invention as an object of research in order to determine a use for the invention, and does not meet the requirement for a specific and substantial utility. *Brenner v. Manson.*

Furthermore, it is unclear whether the reduced PPI observed for the specific transgenic mice with the 129/OlaHsd / C57BL/6 background is due to the protein phosphatase 2C disruption. The specification does not disclose the nature of the wild-type control mice to which the mutant mice were compared in assessing phenotypes. If the wild-type control mice were litter mates of the mutant mice, then the control mice would be homozygous for the C57BL/6 genes linked to the wild type allele of the disruption.

Several sources of unpredictability arising in assessing the phenotype of transgenic knock-out mice have been recognized in the prior art that raise doubts as to whether the phenotype of a specific knock-out mouse is characteristic of all knock-out mice carrying a disruption in the same gene. First, as disclosed in the specification if the targeting vector includes a heterologous gene, e.g. a marker gene, transcription of the heterologous gene may affect

expression of nearby genes. If so, then one cannot determine whether an observed phenotype is due to the inactivation of the targeted gene, e.g.protein phosphatase 2C, or to alteration in expression of a nearby gene due to the presence of the heterologous gene in the targeting vector.

Second, the laboratory environment in which the mice are kept and studied may have an effect on observed behavioral phenotypes. The difference in degree of many behavioral phenotypes between mice of different genetic backgrounds can differ between laboratories (see Crabbe et al., Science 284: 1670-1672, June 1999). Thus, the phenotype of the disrupted protein phosphatase 2C mice relative to the "wild-type control" mice observed by Applicant in their laboratory, may not be reproducible if the relative phenotype were assessed by another skilled in the art, in their laboratory, even when all other factors are the same.

Finally, it is widely recognized that the different inbred strains of mice commonly used to make knockout mice vary widely in behavioral characteristics and neuroanatomy. Consequently, the specific genetic background of the strains of mice used to create or present in a knock-out mouse can be responsible for or contribute to a phenotype observed in the knock-out mouse (Silva et al., Neuron 19 (4): 755-759, Oct. 1997; Gerlai, R., Trends in Neurosci. 19 (5): 177-181, May 1996; Crawley et al. Psychopharmacology 132 (2): 107-124, July 1997; Bampton et al., Brain Res. 841 (1-2): 123-134, Sep. 1999; Nature 415: 8-9, Jan. 2002). A phenotype observed may have nothing to do with inactivation of the targeted gene, but may be the result of genetic differences in the genes linked to the targeted gene. This problem can be exacerbated by

comparing an F2 knock-out mouse to a F2 wild type littermate, since the genotypes for genes linked to the targeted gene will be also be homozygous in both cases. However, the genotypes of linked genes in the knock-out mouse will be that of the strain from which the ES cell was derived, whereas the genotypes of linked genes in the wild-type littermate will be that of the mouse strain to which the chimeric mice were crossed (see Gerlai, Fig. 1). Also, the phenotype may be influenced by the disruption mutation, but also depend upon the genotypes of other genes present in a particular background. Furthermore, the genetic background will differ substantially from that of either parent, being a mixture of the two. Gerlai (page 179, col. 1) discloses that 129 mice display a variety of differences in behavior and neuroanatomy compared to other inbred mouse lines, including in performance in a rotorod test. Crawley (page 108, col. 1) discloses that both 129 and C57BL/6 are unusual in many behavioral paradigms. Both Crawley (Table 4, page 112) and Paylor (Fig. 1) disclose that PPI is highly variable between different strains of mice, with C57BL/6J showing the lowest PPI among all strains tested. Bampton (page 124, col. 1) teaches that the combination of 129 Ola and C57BL/6, used by applicant, is particularly problematic due to their differences, and that phenotypic characterization of the parent strains is "an essential precursor" to studies of mutant mice made from these strains. Such characterization of 129/OlaHsd and C57BL/6 is not reported in the instant specification. For example, one or more of the disclosed phenotypes may be typical of the 129/OlaHsd parent or the C57BL/6 parent, relative to the unspecified "wild-type" control.

The experiments described in the instant specification do not include controls for any of the recognized sources of unpredictability in ascribing a particular phenotype to a specific disruption. The influence of the targeting vector was not assessed, the effect of the environment on the phenotypes was not assessed, the effect to the genetic background was not assessed, and the contribution of genes linked to protein phosphatase 2C was not assessed. The failure to disclose the identity of "wild-type control mice" precludes any evaluation of whether the observed phenotypes are within the normal range of variation seen between "wild-type" inbred mouse strains, i.e. it cannot be determined whether any of the phenotypes are mutant. Consequently, there is no way for one of skill in the art to determine from the specification whether the reduced PPI phenotype disclosed in the specification for the F2 generation 129/OlaHsd/C57BL/6 protein phosphatase 2C- mice are characteristic of a genus of protein phosphatase 2C homozygous knockout mice, or whether the observed phenotype was an artifact of the specific mice made and/or the choice of wild type control mice. Consequently, there is no evidence of record that the claimed transgenic mouse is different in any meaningful way from any other mouse with respect to a reduced PPI phenotype or that the disruption of protein phosphatase 2C was responsible for the reduction in PPI. Consequently, the use for the mouse in screening compounds for potential use in treating schizophrenia based on the PPI phenotype is not a specific utility.

The specification (page 7, lines 1-8; page 23, lines 7-22) asserts a vague and nebulous use for the claimed transgenic mouse and cells for identification of agents that affect the expression or function of PP2C, which involves comparing the effect of such a compound on the claimed mouse to a wild-type mouse or an untreated transgenic mouse. The claimed transgenic mice and cells homozygous for the disruption do not express BNaC2. Consequently, if a compound had an effect on the claimed mouse, the effect would not be relevant to expression or activity of BNaC2. It is therefore unclear how comparison to an untreated claimed mouse would provide any useful information regarding protein phosphatase 2C Conceivably, comparing the effect of the compound on the claimed mouse or cell as compared to wild-type might be used to identify a compound that directly or indirectly affected protein phosphatase 2C expression or activity. protein phosphatase 2C had been partially characterized at the biochemical level. In order for such a method to have a specific and substantial utility, the compounds identified as affecting protein phosphatase 2C expression or activity would have to meet the requirements for a specific and substantial utility, *In re Kirk*, 153 USPQ 48 (CCPA 1967). The specification discloses no such compounds, nor does it identify a use for such compounds. Once having identified such compounds, one would then have to identify a use for them that provided some benefit to the public in a real world context, e.g. treating a disease. Using the compounds for further study of protein phosphatase 2C would not accomplish this, *Brenner v. Manson*.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 26-36 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

In addition to the reasons set forth above, the specification fails to enable using the claimed transgenic mouse or cell for identifying compounds that affect the function of protein phosphatase 2C for the following reasons. Many types of protein phosphatases are known in the art and generally 'are implicated in the molecular mechanism by which extracellular signals regulate extracellular functions' (Klump *et al.* page 328, bridging first and second columns). Protein phosphatases are classified into families by specific biochemical criteria where PP2C members are classified by their dependence on Mg2+ (Klump *et al.* page 328, middle of second column). Protein phosphatase 2 C expression and activity of various isozymes has been characterized in detail for its role in various animal tissues. For example, Travis *et al.* teach that protein phosphatase 2 C can dephosphorylate cystic fibrosis transmembrane conductance

regulator (CFTR). While Travis *et al.* teach that experimental evidence indicates that protein phosphatase 2 C is implicated in CFTR control, the importance of 'PP2C in regulating CFTR appears to differ among tissues' and 'may reflect differential localization or regulation of the phosphatases in different cell types' (page 11059, second column). Travis *et al.* conclude 'that little knowledge of how the activity of PP2C is governed' and suggest the need to identify the molecular basis for PP2C regulation (page 11059, bottom of second column). Klumpp *et al.* provide similar conclusions for the need to further characterize the various isozymes PP2C (page 337, bottom of second column). However, the conclusion of Klumpp *et al.* is based on studies for the role of PP2C in the retinae (page 328, see summary in abstract). Both Travis *et al.* and Klumpp *et al.* provide evidence for the complicated role of PP2C in signal transduction and its role in a wide variety of tissues *in vivo*. As noted above, the sequence disclosed as SEQ ID NO: 1 in the instant specification is a putative PP2C sequence. The specification silent with respect to any guidance to what isozyme the putative PP2C sequence may represent and provides no characterization of the expression or role of the putative PP2C sequence *in vitro* or in any animal. Examiner acknowledges that disrupting the endogenous gene represented by SEQ ID NO: 1 in the genome of a transgenic knock-out mouse results in an unexpected phenotype of a stimulus processing deficit, an abnormal startle response and a decreased prepulse inhibition. However, in light of the complicated and diverse role of other PP2C isozymes described in the art, in particular PP2C's role in tissues not associated with the brain, it is not clear that disrupting other PP2C isozymes known and described in the art would result in the phenotype recited and

required by the instant claims. Even with respect to the particular phenotype of startle response as measured by prepulse inhibition Paylor *et al.* teach that phenotype may vary among various mouse lines commonly used in the laboratory (page 169, see summary in abstract). Further, Paylor *et al.* teach that each of the phenotypes characterized are not correlative of each other, indicating that the different responses are due to different genetic components (top of page 178). In summary, in light of the diverse and complex role of PP2C isozymes known and described in the art, the specification fails to provide a nexus between the affects of disrupting the gene represented by SEQ ID NO:1 with any other PP2C known in the art. As indicated above, no physiological function was known for the putative protein phosphatase 2C. The specification provides no assays for increased or decreased function of protein phosphatase 2C With the possible exception of assaying PPI, the specification identifies no behavioral or physiological difference between the claimed mice or cells and wild type mice or cells. As pointed out above, it is unclear and unpredictable as to whether the observed PPI reduction in the specific mice examined was related to the disruption of protein phosphatase 2C Consequently, one of skill in the art would be required to conduct trial and error experimentation to identify one or more behavioral or physiological assays in which the claimed mice or cells yield different results than would a wild-type control mouse or cell. Furthermore, the specification identifies no lead compounds that might be expected to affect the function of PP2C, which would also require trial and error experimentation in order to identify such leads. In view of the lack of guidance, the state of the prior art, the nature of the experimentation required, and the lack of working

examples, it would require undue experimentation to use the claimed mice or cells for this purpose.

In view of the lack of guidance, working examples, breadth of the claims, the level of skill in the art and state of the art at the time of the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed.

Claims 26-36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 26-36 are broadly directed to a generic transgenic mice with a homozygous disruption in protein phosphatase 2C which display one or more phenotypes. The specification describes a single species of transgenic mouse, specifically made by the process of disrupting a protein phosphatase 2C gene in an ES cell of 129/OlaHsd using the targeting vector shown in figures implanting the ES cell into a pseudopregnant C57BL/6 mouse to produce chimeric mice; breeding a male chimeric mice to a female C57BL/6 mouse to produce a heterozygous mouse; backcrossing the heterozygous mice to C57BL/6 to produce heterozygous mice; and finally

intercrossing heterozygous mice to produce mice homozygous for the protein phosphatase 2C disruption. Consequently, the specific homozygous -/- mice disclosed are hybrids that are approximately three quarters C57BL/6 and one quarter 129/OlaHsd over the entire genome, and homozygous for 129/OlaHsd genes linked to the disruption site. The specification does not disclose the nature of the wild-type control mice to which the mutant mice were compared in assessing phenotypes. If the wild-type control mice were litter mates of the mutant mice, then the control mice would be homozygous for the C57BL/6 genes linked to the wild type allele of the disruption.

The disclosed F2 homozygous disrupted protein phosphatase 2C 129/OlaHsd/ C57BL/6 mice were found to have the specific phenotype of decreased PPI relative to an unspecified "wild-type control" mouse. Other phenotypic traits were assessed, but the results of these assessments are not disclosed. It is presumed that the homozygous protein phosphatase 2C disruption did not have a phenotype different from wild-type controls in these cases. In addition, one homozygous transgenic mouse had an enlarged thymus, one had an enlarged uterus due to cystic hyperplasia, and some appeared to have reduced weight relative to unspecified wild-type controls

As discussed above, several sources of unpredictability arise in assessing the phenotype of transgenic knock-out mice have been recognized in the prior art that raise doubts as to whether the phenotype of a specific knock-out mouse is characteristic of all knock-out mice carrying a

disruption in the same gene: the effect of expression of the heterologous gene in the disruption on adjacent genes, the influence of environment on observed phenotypes, the wide variation between inbred strains of mice in behavioral characteristics and neuroanatomy, and the influence of the genetic background of specific parental strains on the observed phenotype.

The experiments described in the instant specification do not include controls for any of the recognized sources of unpredictability in ascribing a particular phenotype to a specific disruption. The structure of the targeting vector is not adequately described (see below) and influence of the targeting vector was not assessed, the effect of the environment on the phenotypes was not assessed, the effect to the genetic background was not assessed, and the contribution of genes linked to the protein phosphatase 2C was not assessed. The failure to disclose the identity of "wild-type control mice" precludes any evaluation of whether the observed phenotypes are within the normal range of variation seen between "wild-type" inbred mouse strains, i.e. it cannot be determined whether any of the phenotypes are mutant. Consequently, there is no way to for one of skill in the art to determine from the specification whether the phenotypes disclosed in the specification for the F2 generation 129/OlaHsd/C57BL/6 protein phosphatase 2C- mice are characteristic of a genus of protein phosphatase 2C homozygous knockout mice. In order to determine whether any of the disclosed phenotypes are characteristic of a homozygous protein phosphatase 2C disruption, one would have to carry out unguided trial and error experimentation using different targeting vectors, different mouse lines

for ES cells and for the strain being crossed into, and carry out substantial back-crosses to determine which, if any, of the disclosed phenotypes can be reproduced in a variety of mouse backgrounds. Therefore, one of skill in the art would not accept that Applicant was in possession of a claimed genus of transgenic mouse displaying a reduced PPI phenotype, and it would require undue experimentation make such a genus since it has not been established that the disruption of protein phosphatase 2C is responsible for the phenotype and trial and error experimentation would be required to identify different backgrounds having a BNaC2 disruption that would also show the PPI phenotype.

While Applicant was in possession of a F2 generation 129/OlaHsd/C57BL/6 protein phosphatase 2C- mouse that displayed a lower PPI relative to an unspecified wild-type control, the contribution to the observed phenotypes of the specific targeting vector used was not assessed, and the specification does not disclose the "wild-type" control mouse to which one can compare the phenotypes. As admitted in the specification, one cannot determine whether the phenotype resulted from gene inactivation or insertion of a heterologous gene. Consequently, there is sufficient reason to believe that one or more of the disclosed phenotypes may have been due to the heterologous gene included on the targeting vector. One cannot reproduce the same mice described in the specification because the specification does not describe the LacZ-Neo cassette of the targeting vector (Fig. 5) in sufficient detail to allow one to make it. For example, the specification does not disclose the transcriptional regulatory sequences present and the transcriptional orientation of the cassette relative to the flanking protein phosphatase 2C

sequences. The targeting vector encompassed by the definitions for biological material set forth in 37 C.F.R. § 1.801. Because it is apparent that this biological material is essential for practicing the claimed invention, it must be obtainable by a reproducible method set forth in the specification or otherwise be known and readily available to the public as detailed in 37 C.F.R. §§ 1.801 through 1.809.

It is unclear whether this biological material is known and readily available to the public or that the written instructions are sufficient to reproducibly construct this biological material from starting materials known and readily available to the public. Accordingly, availability of such biological material is deemed necessary to satisfy the enablement provisions of 35 U.S.C. § 112. If this biological material is not obtainable or available, the requirements of 35 U.S.C. § 112 may be satisfied by a deposit of the biological material. In order for a deposit to meet all criteria set forth in 37 C.F.R. §§ 1.801-1.809, applicants or assignee must provide assurance of compliance with provisions of 37 C.F.R. §§ 1.801-1.809, in the form of a declaration or applicant's representative must provide a statement. The content of such a declaration or statement is suggested by the enclosed attachment. Because such deposit will not have been made prior to the effective filing date of the instant application, applicant is required to submit a verified statement from a person in a position to corroborate the fact, which states that the biological material which has been deposited is the biological material specifically identified in the application as filed (37 C.F.R. § 1.804). Such a statement need not be verified if the person is

an agent or attorney registered to practice before the Office. Applicant is also reminded that the specification must contain reference to the deposit, including deposit (accession) number, date of deposit, name and address of the depository, and the complete taxonomic description. Evidence that the specific targeting vector used had no effect on the reduced PPI observed in the 129/OlaHsd/C57BL/6 background would obviate the deposit requirement.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims rejected under 35 U.S.C. 103(a) as being unpatentable over Capecchi *et al.* (US Patent 5,464,764) and Hou *et al.* (Biochem Mol Biol Int 32(4)773-380, 1994) is withdrawn.

Cancellation of the claims has rendered the rejection moot. With respect to the newly added claims, it is noted that each claim includes a limitation that the disrupted sequence comprise SEQ ID NO:1. A sequence homology comparison of SEQ ID NO: 1 and those disclosed by Hou *et al.* indicates that the PP2Csequences disclosed by Hou *et al.* do not comprise

SEQ ID NO: 1. The instant claims are not obvious over Capecchi *et al.* and Hou *et al.* because the cited references do not teach every limitation encompassed by the claims.

Conclusion

No claim is allowed. Claims 26-36 are free of the art of record. In particular, various PP2C sequences were known and characterized at the time of filing, and from the characterization of these PP2C genes there was no suggestion that a disruption in a PP2C gene in a transgenic animal would result in the phenotype of a stimulus processing deficit and abnormal startle response as set forth in the claims. Further, it is noted that the sequence set forth in Genebank AF117832 is the same as reduced to practice in the instant disclosure, however the sequence represents a putative PP2C polynucleotide sequence and because of the unpredictability of the art of transgenics there would have been no motivation to disrupt a gene represented only by a partial EST of a putative gene sequence or the expectation of success for any predicative or useful phenotype in a resulting transgenic animal. Finally, it is noted that a stimulus processing deficit and abnormal startle response are phenotypes observed in patients with schizophrenia thus, transgenic animals demonstrating these phenotypes could serve as models for future drug discovery.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (703)305-3732. After January 12, 2004, the Examiner's telephone number will be (571) 272-0739.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (703) 305-4051. After January 12, 2004, Deborah Reynolds telephone number will be (571)272-0734.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (703) 308-2141. After January 14, 2004, Dianiece Jacobs telephone number will be (571)272-0532.

Joseph T. Woitach